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**BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES**

Application Number: 09/382,837
Filing Date: August 25, 1999
Appellant(s): BORODIC, GARY E.

Enrique Longton
For Appellant

**EXAMINER'S ANSWER**

This is in response to the appeal brief filed 11/22/06 appealing from the Office action mailed 10/13/05.

**(1) Real Party in Interest**

A statement identifying by name the real party in interest is contained in the brief.

**(2) Related Appeals and Interferences**

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

**(3) Status of Claims**

The statement of the status of claims contained in the brief is correct.

**(4) Status of Amendments After Final**

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

**(5) Summary of Claimed Subject Matter**

The summary of claimed subject matter contained in the brief is deficient. 37 CFR 41.37(c)(1)(v) requires the summary of claimed subject matter to include: (1) a concise explanation of the subject matter defined in each of the independent claims involved in the appeal, referring to the specification by page and line number, and to the drawing, if any, by reference characters and (2) for each independent claim involved in the appeal and for each dependent claim argued separately, every means plus function and step plus function as permitted by 35 U.S.C. 112, sixth paragraph, must be identified

and the structure, material, or acts described in the specification as corresponding to each claimed function must be set forth with reference to the specification by page and line number, and to the drawing, if any, by reference characters. The brief is deficient because, as set forth below in the rejections for lack of adequate written description, the specification does not support the method of the instant claims. Accordingly, Appellant cannot accurately cite support in the specification because said support does not exist.

**(6) Grounds of Rejection to be Reviewed on Appeal**

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

**(7) Claims Appendix**

The copy of the appealed claims contained in the Appendix to the brief is correct.

**(8) Evidence Relied Upon**

6,063,768 FIRST, E.R. 16 May 2000

THE MERCK MANUAL, 16th Edition, BERKOW, editor. 1992; pages 318-320, 1308-1311, and 2368.

**(9) Grounds of Rejection**

The following ground(s) of rejection are applicable to the appealed claims:

1. Claims 10-12 are rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent No. 6,063,768 (filed 9/04/97) in view of The Merck Manual (1992).

The '768 patent teaches a method of reducing neurogenic inflammation by inhibiting at least one neurogenic inflammatory mediator (such as substance-P) by interrupting a neurogenic pathway, comprising administering a botulinum toxin type A chemodenervating agent to an anatomic region in a dose of 5 LD 50 units or at a dose of 1000 units, in conjunction with other anti- inflammatory agents (inflammatory antagonists). Further, the reference teaches the treatment of inflammatory disorders including rheumatoid arthritis and gout, and the inhibition of histamine (see particularly column 2, lines 34-60, columns 5-7, and Claims 1-6).

The '768 patent differs from the claimed invention in that it does not teach a method of reducing inflammation due to blepharoconjunctivitis, hay fever, rhinitis, or type 1 hypersensitivity. Neither does the '768 patent teach the use of other anti-inflammatory agents comprising steroids or non-steroids.

The Merck Manual teaches that blepharoconjunctivitis, hay fever, rhinitis, and type 1 hypersensitivity are inflammatory disorders amenable to treatment by anti-inflammatory agents (see particularly pages 318-320 and 2368). The reference further teaches that steroidal and non-steroidal drugs are common anti-inflammatory agents (see particularly pages 1308-1311).

From the teachings of the references it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to perform a method of reducing

neurogenic inflammation by inhibiting at least one neurogenic inflammatory mediator comprising administering a botulinum toxin type A chemodenervating agent to an anatomic region, in conjunction with other anti-inflammatory agents, as taught by the '768 patent, substituting a steroidal and non-steroidal drug as the specific additional anti-inflammatory agent, as taught by The Merck Manual for the treatment of inflammatory conditions such as blepharoconjunctivitis, hay fever, rhinitis, and type 1 hypersensitivity, as taught by The Merck Manual. One of ordinary skill in the art would have been motivated to make said substitutions because blepharoconjunctivitis, hay fever, rhinitis, and type 1 hypersensitivity are inflammatory disorders amenable to treatment by anti-inflammatory agents, as taught by The Merck Manual, and steroidal and non-steroidal drugs are common anti-inflammatory agents, also taught by The Merck Manual.

2. Claims 1, 5-8, 24, 25, 42, 43, and 46-57 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

a method of reducing allergy induced conjunctivitis in a mouse comprising administering a botulinum toxin,

does not reasonably provide enablement for:

a method of reducing inflammation without causing muscle weakness.

The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation. The scope of the

claims is not commensurate with the enablement provided by the disclosure.

The critical element of the claims is the extremely low dose of the toxin that might still retain anti-inflammatory effects. The specification, however, discloses only one rat example (CONJUNCTIVITIS) in which the toxin is used at such a low dosage. It is noted that in all the human examples the toxin is used in at least a dosage of 2.5 units. Additionally, in each human example, the toxin is used at a dosage specifically *intended* to cause muscle weakness and the anti-inflammatory properties are merely observed as a side effect (see particularly Case I and Case II). As such, the claim of a method employing an effective dose of botulinum toxin for reducing inflammation without causing substantial muscle weakness is mere assertion, said assertion being highly unpredictable as the method is not recognized in the art as a method of reducing inflammation (see The Merck Manual, 1992, pages 318-320). Said method would require significant enablement, i.e., working examples, given said unpredictability.

*In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. Thus, in view of the quantity of experimentation necessary, the lack of sufficient working examples, the unpredictability of the art, and the lack of sufficient guidance in the specification regarding both how to both make and use the claimed invention, it would take undue trials and errors to practice the claimed invention.

Further (from the rejection of 9/25/03), regarding "treating inflammation with a chemodenervative pharmaceutical, such as botulinum toxin, without causing muscle weakness", the specification simply does not disclose that said parameter (muscle weakness) was measured. Regarding the spasmodic torticollis example, it is noted that the example does not actually disclose that any specific dosage of any specific toxin results in any specific outcome. Indeed, it is unclear whether the example is intended to disclose experimental results or merely representative results. Note the actual wording of the example "Botulinum toxin injected into red areas noted to be painful and thermally active in accordance with the subject invention has been demonstrated to block the erythema, pain, increased tenderness, and heat loss within the area consistent with the denervation diffusion potential for the given dose, as can be seen in Figures 8A and 8B, in which Figure 8A shows the red patch and Figure 8B shows a blanched area of blocked inflammation at the injection site. Minimum doses range between 0.6 units to 15 units and are far lower than that required to produce regional weakness" (underlining added by Examiner). Note the use of the somewhat vague phrase "has been demonstrated". There is no indication that said demonstration is actually in the form of an experiment performed as a working example for inclusion in the instant application. Indeed, the example never actually discloses that the procedure was performed nor that any specific dosing regimen was used. The employed wording could simply mean that the results of the figures might represent what would be expected to happen if the

method of the claims was performed. Accordingly, this "example" cannot support the limitations of the claims.

3. Claims 1, 5-8, 10-12, 21-25, and 42-57 are rejected under 35 U.S.C. § 112, first paragraph, as the specification does not contain a written description of the claimed invention, in that the disclosure does not reasonably convey to one skilled in the relevant art that the inventor(s) had possession of the claimed invention at the time the application was filed. This is a new matter rejection.

The specification and the claims as originally filed do not provide support for the invention as now claimed, specifically:

A) A method of reducing inflammation, comprising the step of administering a therapeutically effective dose of a botulinum toxin to an affected area of a subject suffering from inflammation, wherein the botulinum toxin reduces at least one symptom of inflammation and wherein said therapeutically effective dose is sufficient to reduce said at least one symptom of inflammation but less than a dose necessary to produce substantial muscle weakness within the affected area (Claim 1).

B) A method of treating allergic blepharoconjunctivitis comprising the step of administering a therapeutically effective dose of a botulinum toxin in a periocular area of a subject suffering from blepharoconjunctivitis, thereby reducing inflammation (Claim 10).

C) A method of treating classic type I hypersensitivity comprising the step of administrating a botulinum toxin to an affected area of a subject suffering from classic type I hypersensitivity, thereby reducing inflammation (Claim 11).

D) The method of Claim 11 whereby the hypersensitivity is hay fever, rhinitis, allergic rhinitis, allergic forms of eczema, urticaria, rheumatoid arthritis, inflammatory bowel disease, or asthma (Claim 12).

E) A method for treating inflammation, comprising the step of administering a botulinum toxin to an affected area in a therapeutically effective dose sufficient to reduce a rapid-phase response under neural regulation thereby reducing at least one symptom of inflammation, and wherein said therapeutically effective dose is sufficient to reduce the at least one symptom of inflammation but less than a dose necessary to produce substantial muscle weakness within said affected area (Claim 24).

F) The limitations of new Claims 42-57 as further limiting of Claims 1, 10, 11, and 24.

Applicant indicates that support for: A) can be found at pages 3, 4, 8, and 20; B) can be found at page 15; C) can be found at pages 11 and 12, and original Claim 12; D) can be found at page 12; E) can be found at pages 3, 4, 7, and 8; new Claims 42 and 43 at pages 9, 15, and 20; new Claims 46-48 at pages 4, 6, and 7; new Claim 49 can be found at page 12; new Claim 50 can be found at page 16; new Claims 52-53 can be found at page 3 and

4, and original Claim 2; and new Claims 54-57 at page 20 of the specification.

A review of the specification and original claims reveals that essentially no support can be found in the various cites for the limitations of the new and amended claims. First note that the cites in the Background section (pages 2-4) do not support the claimed method because neither the claimed method of the independent claims, nor any of the limitations of the dependent claims as they apply to the invention, are disclosed in the Background; if they were it would not be "background" but rather a description of the invention. Returning to the invention of Claim 1, page 8 of the specification discloses no actual method, but merely a vague teaching that, "In one embodiment, the effective dosage for allergy provoked inflammation reduction is an order of magnitude less than dosages associated with treatment of regional movement diseases, since the agent works to reduce inflammation by reducing histamine and other preformed mediator releases associated with mast cell degranulation. The effects recognized herein give new utility to chemodenervating agents." At page 20 the specification discloses only the partial results of a botulinum toxin-treated spasmodic torticollis patient and not the generic method of the claim. Similarly, the other cites do not support the newly claimed method.

**(10) Response to Argument**

In part **A.** (for lack of enablement), Appellant argues that the rejection is improper for at least the following reasons: (1) the Office has not met its burden of establishing a *prima*

*facie* case of lack of enablement because four of the eight *Wands* factors have not been considered by the Office; (2) no experimentation would be required to practice the claimed invention and the Office bases its determination of lack of enablement on conclusory statements that ignore or discount what is taught in the specification; and (3) the Office has provided no evidence to support its position that the statements made in the specification should not be accepted. Applicant respectfully asserts that the rejection is therefore improper and should be withdrawn.

Regarding (1), MPEP 2164.04 states:

> While the analysis and conclusion of a lack of enablement are based on the factors discussed in MPEP § 2164.01(a) and the evidence as a whole, it is not necessary to discuss each factor in the written enablement rejection. The language should focus on those factors, reasons, and evidence that lead the examiner to conclude that the specification fails to teach how to make and use the claimed invention without undue experimentation, or that the scope of any enablement provided to one skilled in the art is not commensurate with the scope of protection sought by the claims.

Accordingly, only the most appropriate *Wands* factors have been discussed.

Regarding (2), Appellant's assertion that *no* experimentation would be required to practice the claimed invention simply flies in the face of scientific reality.

Regarding (3), Appellant's argument that the Office has provided no evidence to support its position that the statements made in the specification should not be accepted, MPEP 2164.03 makes clear that physiological activity is generally considered

to be *inherently* unpredictably. Thus, enablement in excess of mere assertion that an invention works is required. Indeed, MPEP 2164.03 states:

> In applications directed to inventions in arts where the results are unpredictable, the disclosure of a single species usually does not provide an adequate basis to support generic claims.

In this instance *no* examples, not even a single species, demonstrating the method of the instant claims have been provided.

In part **a.** of the arguments (in response to the rejection for lack of enablement), Appellant asserts that page 19 provides enablement for the scope of the breadth of the claims.

Page 19 of the specification states:

> Computed Tomography Findings In Idiopathic Spasmodic Torticollis, Mov Disord 1997 Jan;12(1):79-88.
>
> As illustrated in Figures 7A-D, it has been discovered and is a part of the subject invention that an important clinical sign, not previously described in the medical literature, is associated with the syndrome. This sign involves the formation of red patches noted on the skin, often associated with painful areas, best demonstrated with red wavelength sensitive photography. Here, four patients with cervical dystonia were diagnosed with red patches. This sign involves the formation of red patches noted on the skin often associated with painful areas. These areas are generally warmer to touch, and not associated with any intrinsic skin changes such as scaling, crusting or any signs of cutaneous inflammation or cell proliferation. It has been found that these changes are more prominent in patients with cervical dystonia who are having more difficulty with pain. These patches typically occur posterior to the scalene muscle and inferior to the ear, although they have been seen over the trapezius and sternomastoid muscle. The red patch has been found to represent an area of maximal tenderness, and provides evidence that inflammation is an integral component of the spasmodic torticollis syndrome. Moreover, the red patch indicates that spasms inherent in the torticollis syndrome are driven at least in part by the inflammatory process, and that pain occurring in torticollis is, in part, inflammatory in nature. Additionally, the red patch indicates that inflammation in torticollis in peripheral tissues may be neurogenically mediated, and that proprioceptive information to the

> brain leaving muscles is to some degree mediated by elements of neurogenically provoked inflammation or inflammation associated autocoids.
>
> Botulinum toxin injected into red areas noted to be painful and thermally active in accordance with the subject invention has been demonstrated to block the erythema, pain,

It is unclear how the disclosure of this page can be said to enable the method of the instant claims.

Appellant cites pages 2-4 in support of the claimed method.

Pages 2-4 of the specification comprise the Background of the Invention. If the invention were adequately disclosed and enabled there it would have been because the invention was found in the prior art. Save the method of Claims 10-12, it is not.

Appellant cites pages 10-20 in support of the claimed method.

No where at pages 10 -20 does the specification disclose that Appellant actually measured for the claimed invention, i.e., a method of reducing inflammation without causing muscle weakness.

Appellant cites page 17 of the specification and seems to imply that the cite provides enablement for the claimed method.

Page 17 of the specification states:

> analogue scale pre-injection and 2-3 weeks after injection in an open label study. In a series of 14 patients, the effects on photophobia were reported to be significantly mitigated ($p<0.05$). Here, the anti-inflammatory mechanism of the subject agent is clearly active.
>
> TREATMENT OF INTERNAL INFLAMATORY DISEASES

> In the past, it was thought that the tissue mechanisms associated with using chemodenervating agents have solely involved the use of botulinum toxin as a means of causing muscle relaxation or to produce certain autonomic effects blocking decreased sweating. Although there have been conditions treated by chemodenervating agents which have had associated inflammatory reaction as a part of the clinical syndrome, the concept of muscle relaxation induced by such agents has been thought to be the mechanism by which such agents induce the beneficial effects. It has now been found that the subject agent has useful anti-inflammatory properties capable of blocking ocular surface allergic inflammation in man and animal models, as well as generalized inflammation within the denervation field created.
>
> For treatment, the practitioner defines a fixed anatomic area in which symptomatic and/or destructive inflammatory processes are occurring. Knowledgeable of dose related diffusion properties and potency of the preparation being used, the practitioner defines the anatomic area to be treated. Avoiding critical structures, e.g. blood vessels, nerves and anatomic cavities, the practitioner injects a fixed dosage of the chemodenervating agent so as to create a denervation field, reducing the intensity of tissue destruction occurring within the area of treatment. Such a field can be defined internally, e.g. stomach mucosae-gastritis, joint-arthritis and muscle myositis. Follow-up involves monitoring for the cardinal sign of inflammation-pain redness, edema and discharge. Adjuvant therapy with other anti-inflammatory agents would be contemplated.

It is again unclear how the disclosure of this page can be said to enable the method of the instant claims.

In part **B.** of the argument (in response to the rejection for obviousness), Appellant argues that the references do not render the claims obvious. Appellant argues that neither of the references alone renders the claimed method obvious.

Clearly, it is the combination of references and the "knowledge generally available to one of ordinary skill in the art" (MPEP 2143.01), that renders the claimed method obvious as is set forth in the rejection.

Appellant argues, "The Office Action alleges that "one of ordinary skill in the art would have been motivated to make the said substitutions because blepharoconjunctivitis, hay fever, rhinitis, and type 1 hypersensitivity are inflammatory disorders amenable to treatment by anti-inflammatory agents, as taught by the Merck Manual, and steroidal and non-steroidal drugs are common anti-inflammatory agents, also taught by the Merck Manual." Office Action at page 7. Applicants respectfully disagree."

Note that Appellant provides no actual argument here; Appellant simply "disagrees".

In part **C.** of the argument (in response to the rejection for lack of adequate written description), Appellant cites original Claim 2, and pages 3, 4, and 19 in support of Claim 1.

Original Claim 2 recites:

> A method of treating inflammation, comprising the step of administering a chemodenervating agent to an anatomic region in a dose just sufficient to reduce inflammation, but below that necessary to cause substantial muscle weakness.

Clearly, limitations now recited in the claim, e.g., "… wherein said therapeutically effective dose is sufficient to reduce said at least one symptom of inflammation …", are not found in original Claim 2, nor in the Background section of the specification (pages 3 and 4). At page 19 of the specification is found a description of part of a single experiment employing a spasmodic torticollis patient that cannot support the generic method of Claim 1.

Appellant argues the support for Claims 5-8 can be found throughout the specification and in original Claims 5-8.

The limitations of Claims 5-8 are not disclosed in the specification, nor recited in the original claims, in the context of dependency from Claim 1 as now recited.

Appellant cites original Claim 10, and pages 7, 15, and 20, as well as Figures 3-6, in support of Claim 10.

None of the cites disclose or recite the limitation of the claim of "... reducing inflammation".

Appellant cites original Claim 11, and pages 5, 20, and 13, as well as Figures 3-5, in support of Claim 11.

None of the cites disclose or recite the limitation of the claim of "... reducing inflammation".

Appellant cites original Claim 12, and pages 6 and 10-13, as well as Figures 3-5, in support of Claim 12.

Claim 12 depends from Claim 11, and thus must include the limitations of Claim 11, i.e., all of the diseases of Claim 12 must be disclosed in the specification or claims as filed as "classic type I hypersensitivity" conditions. Only "hay fever" and "rhinnitis" [sic] are disclosed in this sense. Further, the specification discloses "allergic rhinnitis" [sic] (not the "allergic rhinitis" of the claim) and "allergic eczema" only in

the context of mast cell reactivity and not in the context of the method of the claim.

Appellant cites original Claim 2, and pages 3, 4, 7, and 19, in support of Claim 24.

The issue with this claim is whether or not Appellant can pick and choose limitations found at different points throughout the specification to cobble together a claimed method that is not supported anywhere in the specification as a whole. It appears that Appellant's argument is that one limitation of the claim might be found in original Claim 2, which certainly does not recite any limitations of the claim other than a dosage "below (less than) that necessary to cause substantial muscle weakness", while another limitation might be found under a discussion of mast cells, i.e., "a response under neural regulation". It is the Examiner's position that this does not comprise adequate support for the claimed method. Further note that no support has been offered or found for other limitations, e.g., administration of the botulinum toxin to "an affected area" or the reduction of "at least one symptom of inflammation … within said affected area".

Appellant cites original Claims 2 and 10, and pages 14 and 20, in support of Claim 42.

Appellant has improperly added the limitation of Claim 10 to Claim 2 (from which Claim 10 does not depend) thus creating a new set of limitations not supported by the specification nor claims as filed.

Appellant cites original Claim 2 in support of Claim 43.

Original Claim 2 does not support the limitations of Claim 11 (from which Claim 43 depends), e.g., a method for treating classic type I hypersensitivity.

Appellant cites page 7 in support of Claims 44 and 45.

Page 7 of the specification does not disclose botulinum toxins at all. Additionally, nowhere in the specification nor claims as filed can the use of botulinum toxins A-G be found in the in the context of Claim 10 (from which Claim 44 depends) or Claim 11 (from which Claim 45 depends).

Appellant cites original Claim 8 and page 7 in support of Claim 46.

Original Claim 9 recites a method of "blocking" mast cell degranulation and not a method that "reduces" mast cell degranulation as is claimed. Additionally, the method is not disclosed nor recited in the specification nor claims as filed in the context of Claim 24 (from which Claim 46 depends).

Appellant cites page 7 in support of Claim 47.

Page 7 of the specification does not disclose the limitations of the claim. At page 8 is disclosed, "mast cells degranulating autocoid releases activated by either non-immunologic or immunologic- based processes", which is clearly a

much more limited disclosure than is the generic "mast cell is activated by either non-immunologic or immunologic-based processes" of the claim.

Appellant cites page 4 in support of Claim 48.

No part of the claimed method is disclosed at page 4 of the specification which indeed, is part of the Background section of the specification and discloses none of the claimed invention.

Appellant cites pages 6, 7, and 11 in support of Claim 49.

At page 7 luekotrienes and prostaglandins are disclosed only in the context of mast cell activation and not in the context of the claimed method. At page 12 the specification discloses the factors of the claims as preformed or newly formed mediators only in the context of uticaria. Nowhere are the factors disclosed or recited in the context of the method of the instant claim.

Appellant cites page 16 in support of Claim 50.

Page 16 of the specification discloses allergic blepharoconjunctivitis and blepharospasm. No method of reducing generic ocular surface allergic inflammation is disclosed.

Appellant cites original Claim 2 and page 3 in support of Claims 51-53.

Original Claim 2 and page 3 of the specification do not disclose the limitations of the instant claims in the context of Claim 24 (from which Claim 51 depends), Claim 10 (from which Claim 52 ultimately depends) or Claim 11 (from which Claim 53 ultimately depends).

Appellant cites pages 4, 8, and 20 in support of Claims 54-57.

Page 21 fails to disclose the listed "properties associated with and characterizing inflammation" in a context of reducing said inflammation without producing substantial muscle weakness as is claimed. As set forth above, page 4 of the Background section of the specification discloses nothing regarding the claimed method. Nothing regarding the limitations of the claims is disclosed at page 8 of the specification. At page 9 in the Brief Description of the Drawings is disclosed a photograph assertedly showing that a uticaria patient displayed "a reduction in inflammatory reaction" after injection of a "chemodenervating agent". Said disclosure comprises an insufficient description of the method of Claims 54-57.

**(11) Related Proceeding(s) Appendix**

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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2/23/07
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